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A review on metastatic breast cancer in Iran

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ABSTRACT

Metastatic breast cancer is a disease of early breast cancer that usually occurs several years after the early breast cancer. Breast cancer is the most common cancer among Iranian women. According to the new statistics in Iran 6160 breast cancers are diagnosed in the country each year and 1063 cases lead to death. In this paper, epidemiology, diagnosis and treatment have been investigated. In this study, case–control clinical trials and open studies with adequate data were collected. Due to the higher risk of age group 40–49 years and the advent of advanced breast cancer in Iranian women, the early diagnosis and determination of the exact size of the tumor before surgery is important in choosing a therapy plan. The decision on the therapy of invasive breast cancer depends on several factors such as cancer stage, tumor size and type, pathological and cytological status of the tumor, the patient's opinion, the presence or absence of estrogen and progesterone receptors in the cytoplasm of tumor cells and so on.

1. Introduction

Metastatic breast cancer is a disease of early breast cancer that usually occurs several years after the early breast cancer [1]. Breast cancer is the most common cancer among Iranian women (24.4% of all cancers) and its crude incidence is 17.8% according to the statistics of 2005–2006 [2–4]. According to the studies conducted in 2005–2006, the incidence of breast cancer in Iranian women was 13.3% and 10% of all breast cancer cases in Iran observed in Isfahan [5]. According to the report of World Health Organization, the incidence of breast cancer has annually increased by 2% [6]. According to the new statistics in Iran, 6160 breast cancers are diagnosed in the country each year and 1063 cases lead to death [7,8]. Although the incidence of breast cancer in Asian women is low compared to women in western countries, its incidence trend is considered higher. Breast cancer affects the Iranian women at least a decade earlier than women in developed countries and most of the patients with this disease are in the age of 40–49 years old in Iran [9]. According to the statistics in 2007, at the time of diagnosis, 18% of patients were in stage I, 57% in stage II, 25% in stage III, 72% of patients had tumors larger than 2 cm and 63% had the involvement of lymph nodes at diagnosis [7]. The symptoms of benign conditions are similar to those found in breast cancer and may cause great concern until evaluated and explained by a qualified health professional [10,11].

In total, about 6% of breast cancers were metastatic at diagnosis (5-year survival rate of 21%). The incidence of metastatic disease is high because many women with this disease live for several years [10]. Distant metastasis is the cause of 90% of deaths from breast cancer [12]. And despite the advances in the diagnosis and therapy of breast cancer, more than 44 000 women die of metastatic disease in the United States [13].

Breast cancer primarily metastasize bones, lungs, regional lymph nodes, the liver and brain [14]. Approximately, 70% of patients with advanced breast cancer have bone metastasis. Bone is the most commonly observed site for distant metastases and is the location of 30%–40% of first tumor recurrence [15]. The women whose first recurrence occurs in skeleton have a better prognosis than those with visceral metastasis to the liver, lungs or brain. Most bone metastases can be successfully controlled for a long time [16–18]. Brain

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metastasis has been observed in 10% of breast cancer patients with metastatic properties [19,20].

Although the objective answers to some chemotherapy regimens are common, but a few number of patients with metastatic disease are treated and the therapy often has significant side effects [21]. Nutrition and diet play an important role in breast cancer and may alter disease progression [22,23]. Several studies have shown that obese women are at a high risk for breast cancer metastasis to distant sites [24–26].

Due to the higher risk of age group 40–49 years and the advent of advanced breast cancer in Iranian women, the early diagnosis and determination of the exact size of the tumor before surgery is important in choosing a therapy plan [27].

2. Diagnosis

Breast exam by doctors or by the women herself and getting mammograms are recommended to all women especially those over 40 years old for screening and early diagnosis. Sonography, magnetic resonance imaging and histopathology tests are needed for diagnosis in the next phases [28,29].

In addition to histopathological diagnosis, molecular and cellular tumor markers can help the diagnosis. Today, particular attention is paid to the use of sensitive, quick and cheap techniques, one of which is the use of tumor markers [30,31]. A small number of tumor markers has been accepted for routine use in breast cancer [32]. For example, mammaglobin has been considered a specific diagnostic marker for breast cancer [33]. In assessing human epidermal growth factor receptor 2 (HER2) and chitinase-3-like protein 1, also known as YKL-40, in patients with early diagnosis of recurrence and breast cancer metastasis, the serum level of these two tumor markers has been increased in patients compared to healthy women [34,35]. In another study, the measurement of angiostatin in the urine of patients with breast cancer is a non-invasive method for the diagnosis of cancer [36].

Results show that there is no a specific correlation between the amounts of serum matrix metallopeptidase 9 and lymphatic metastasis with venous invasion [37]. Thus, for the early diagnosis of breast cancer, plasma levels of this enzyme are more appropriate than its serum levels [38,39]. Cancer antigen 15-3 (CA15-3), carcinoembryonic antigen (CEA) and erythrocyte sedimentation rate are other valid markers [40]. In the study of CEA and CA15-3 level of sensitivity in breast tumors with metastasis to the axillary lymph nodes, tumor marker CA15-3 can be used to identify the presence or absence of metastasis of axillary lymph node in breast cancer. However, CEA does not have an appropriate sensitivity in this context [41,42].

In the study of the correlation between serum and salivary concentrations of HER2/neu, also called c-erbB2, in women with breast cancer, it seems that there is little correlation between serum and salivary concentrations of c-erbB2 in the early stages of breast cancer and also the absence of metastasis [43,44].

Breast cancer is uncommon in men, but has increased in the last 25 years. Breast cancer is diagnosed in men in a higher stage and age. HER2/neu expression is more than women [45,46].

2.1. Diagnostic imaging

According to the studies that have been conducted, sonography is a more reliable diagnostic method in diagnosing the lesions in patients with high density mammography (class 3 and class 4), but mammography is more accurate than sonography in determining the size of the tumor before surgery. Thus, the sonography alone before the surgery is not a suitable means for diagnosing the lymph node metastasis [47,48].

A variety of imaging techniques such as computerized tomography scan, magnetic resonance imaging or positron emission tomography scan can be used for detection of bone metastasis. But none of them is suitable for the diagnosis and evaluation of response to therapy. The use of positron emission tomography scan for evaluating breast cancer recurrence and metastasis was valuable and sensitivity was evaluated as 92%, and specificity as 81% [49,50].

3. Therapy

The decision on the therapy of invasive breast cancer depends on several factors such as the cancer stage, the tumor size and type, pathological and cytological status of the tumor, the patient's opinion, the presence or absence of estrogen and progesterone receptors in the cytoplasm of tumor cells and so on [51,52].

3.1. Stage I: two general therapy methods

Two general therapy methods are: modified radical mastectomy or modified radical mastectomy including total mastectomy and axillary dissection; breast conservation therapy or conservative therapy of breast including lumpectomy and axillary dissection followed by radiotherapy for 5 d a week, for 6 weeks, which is delivered at 4500–5000 centigray [53].

The studies have shown that the percentage of tumor recurrence in both methods is approximately equal and using each of these two methods is different depending on the surgeon and patient. Some investigations evaluated the breast conservation therapy method in terms of the quality of life and mental health of women [54,55].

In both methods, the mammography of the treated patient should be done every 6 months until the surgery becomes stable and once a year after it [56].

3.2. Therapy of locally advanced disease without metastasis (stages IIIA, IIIB)

These patients primarily need chemotherapy and after it surgery, radiation, or both should be performed but the likelihood of tumor recurrence is more than the previous group and is about 30%–50%. The results have shown that the method of excision and radiotherapy is more acceptable than total mastectomy. High-risk patients in this group should be checked every three months and all patients with local recurrence in this group should be checked in terms of visceral and bone metastases and should also be evaluated in terms of systemic chemotherapy and hormone therapy [57,58].

3.3. Stage IV

This stage that has been expanded further from breast and axillary lymph nodes is considered incurable and the life expectancy at this stage is estimated about 24 months but it has been observed that some patients with bone involvement and its

soft tissue especially those who have hormone-sensitive tumors, stay alive for years despite their advanced disease [59]. Therapy at this stage is based on chemotherapy and hormone therapy and the surgery can be done only when the patient's tumor shows specific signs. Although some studies have recommended that the surgery in primary tumors and metastatic sites can help extend the life of these patients and enhance the survival rate [60,61].

3.4. Adjuvant therapy

The adjuvant therapy is used when there are no visible tumors and occur to delay the metastasis and includes chemotherapy or hormone therapy [62,63]. The decision for hormone therapy in patients with metastatic breast depends on the presence or absence of estrogen and progesterone receptors in the cytoplasm of tumor cells. Up to 60% of patients with metastatic breast cancer will respond to hormone therapy if the estrogen receptors are positive and up to 80% of patients with progesterone receptors will respond to hormone therapy, but probably they do not have anything to respond to chemotherapy [64,65].

The previous studies have reported that the status of axillary nodes and whether the patient is postmenopausal or not play a role in the survival of the patient's life, so that the risk of mortality from diseases with the involvement of one to three lymph nodes is twice the patients who do not have any involvement [66]. The recurrence rate in women below 50 years after five years of taking tamoxifen is more than women over 50 years [67].

Today, in some cases of hyperthermia, raising the temperature of the tissue to about 40–43 °C is recommended as an adjuvant therapy [68].

In adjuvant therapy, tamoxifen which is an antiestrogen drug is widely used. The effect of tamoxifen for breast cancer prevention in high-risk people is being studied [69]. Although tamoxifen has different effects on the body, the drug inhibits the estrogen receptors in the body, prevents estrogen conversion to estradiol sulfate and ultimately inhibits the protein kinase. Thus, it causes a slight increase in the risk of endometrial cancer and a series of biochemical changes independent of estrogen receptors in the body, including the effect on the endocrine glands, venous thrombosis and eye problems that should be considered in the long-term consumption of tamoxifen [70,71].

Using other drugs in combination with tamoxifen has had better results although with more toxicity [72].

For example, the use of medroxyprogesterone acetate causes a large weight gain. Other examples could be megestrol and aromatase inhibitors [73,74]. Also, the results of both cyclophosphamide and doxorubicin-based chemotherapy have been reported better than other drugs such as epirubicin [75]. Other methods of adjuvant therapy can be oophorectomy and radiating the ovary that has great influence in increasing the survival rate [76,77].

The decision on the therapy of invasive breast cancer depends on several factors such as the cancer stage, the tumor size and type, pathological and cytological status of the tumor, the patient's opinion, the presence or absence of estrogen and progesterone receptors in the cytoplasm of tumor cells and so on. In total, there have been no proved findings about the use of therapies for these patients and relieving the patient's pain and improving his/her quality of life and above all the patient's opinion on the therapy type must be highly considered.

Conflict of interest statement

We declare that we have no conflict of interest.

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